



Common Drug Review *Patient Group Input Submissions*

sapropterin dihydrochloride (Kuvan) for Phenylketonuria (PKU)

Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.

Canadian PKU & Allied Disorders Inc. — permission granted to post.

CADTH received patient group input for this review on or before March 8, 2016.

CADTH posts all patient input submissions to the Common Drug Review received on or after February 1, 2014 for which permission has been given by the submitter. This includes patient input received from individual patients and caregivers as part of that pilot project.

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations. While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Canadian PKU & Allied Disorders Inc.

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Kuvan (Sapropterin dihydrochloride) for PKU
Name of the patient group	Canadian PKU & Allied Disorders Inc.
Name of the primary contact for this submission:	[REDACTED]
Position or title with patient group	[REDACTED]
Email	[REDACTED]
Telephone number(s)	[REDACTED]
Patient group's contact information:	
Email	info@canpku.org
Telephone	Toll Free: 1-877-CanPKU-1 (1-877-226-7581)
Address	260 Adelaide St. East, #180, Toronto
Website	http://www.canpku.org
Permission is granted to post this submission	Yes

1.1 Submitting Organization

Canadian PKU and Allied Disorders Inc. is a non-profit association dedicated to providing information and support to families and professionals dealing with PKU and similar, rare, inherited metabolic disorders.

1.2 Conflict of Interest Declarations

- a) We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements: CanPKU solicits and receives unrestricted educational grants from vendors of treatment products for PKU and bipterin deficiencies to help fund patient support, outreach, community education & advocacy. We declare sponsorship/funding for 2015 & 2016 from: Nutricia, BioMarin, Cambrooke Therapeutics, VitaFlo, Rx&D, & Innomar.
- b) We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission: N/A

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

Recognizing that treatment of PKU requires the close involvement of expert physicians and their patients and/or caregivers, CanPKU conducted two separate online surveys from Jan 7 to Jan 27, 2016:

1. PKU patients and caregivers (n=298) were contacted through our membership database, social media and a partner patient group in the U.S.A. 297 individuals identified as one of "patient" (n=58), "caregiver" (n=217) or "other" (n=23). "Other" was typically a secondary adult caregiver such as a grandparent, second parent or sibling. Ages of patients were: 0-4 years (n=54), 5-12 years (n= 88), 13-17 years (n= 38), 18-24 years (n=35), 25+ years (n=54). Respondents-by-Country: Canada (n=176),

USA (n= 116), UK (n= 2), Sweden (n=1), Australia (n=1), Germany (n=1). 127 survey participants had experience with Kuvan.

2. Clinicians, including physicians and dietitians who treat PKU (n=8). We sought input on prescribing decisions, key factors contributing to treatment choice, and obstacles to best outcomes. Both surveys contained the use of free-form commentary, scoring options and limited closed questions. Copies of each of these surveys can be provided upon request. Supplemental information regarding PKU, treatments and patient experiences was extracted from www.canpku.org.

2.2 Impact of Condition on Patients

To protect brain function, most children and adults with PKU must follow a special diet that involves strictly controlling the intake of natural protein and drinking a synthetic phenylalanine (phe) -free protein formula. The diet is expensive, laborious and complex. It is very unpleasant and lacks food choices. The diet has a tremendous impact on day-to-day life for patients and caregivers. For children and adolescents it is particularly onerous because it has the effect of segregating them from their peers, leading often to poor compliance.

Ironically, living well with PKU requires exemplary executive function as diet planning is astonishingly complex, record-keeping is onerous, maintaining supplies and monitoring blood Phe levels are time-consuming and require excellent organization skills.

We asked patients/caregivers: **How has PKU had an impact on your life (or on the life of the person under your care)?** 8 choices were provided, with respondents able to “pick all that apply” (n=195). *Difficulties with diet* = 71.28% (n=139). *Difficulty with focus (attention deficit)* = 49.74% (n=97), *Exclusion or difficulties in social settings* = 46.67% (n=91), *Depression or Anxiety* = 40.51% (n=79), *Problems at school related to diet compliance* = 30.26% (n=59), *Learning disabilities* = 26.15% (n=51), *Difficulty forming interpersonal relationships* = 18.46% (n=36), *Difficulties maintaining employment* = 9.23% (n=18).

We asked: **In a typical week, how much time do you spend on the following PKU-related tasks?** (n=231) A list of tasks (developed by an examination of relevant published literature) was provided, along with time measure selections. Average times as follows: *Cooking for Phe-restricted diet* = 4 hrs/wk. *Supervising protein intake* = 4 hrs/wk. *Planning daily Phe intake* = 3+ hrs/wk. *Baking bread or other low protein foods* = 3 hrs/wk. *Weighing foods* = 3 hrs/wk. *Keeping records* = 3 hrs/wk. *Food research* = 2.5 - 3 hrs/wk. *Preparing for social events* = 2.5 - 3 hrs/wk. *Researching PKU* = 2.5 hrs/wk. *Blood testing* = 1.5+ hrs/wk. *Ordering low proteins* = 1.5+ hrs/wk. *Clinic appointments* = 1.5+ hrs/wk. *PKU events* = 1.5+ hrs/wk. *Ordering amino acids* = 1.5+ hrs/wk. **Total Time (average) all tasks = 39 hrs/wk. More than five hours a day.**

We asked patients/caregivers: **What symptoms of PKU have had the most impact on you, or on the person under your care?** 8 choices were provided, with respondents able to “pick all that apply” (n=172). *Behavioural, emotional and social problems* was the top symptom selected by 56.98% (n=98). *Skin rashes/eczema* = 41.28% (n=71). *Psychiatric disorders (including panic attacks, depression and phobias)* = 31.98% (n=55). *Hyperactivity* = 28.49% (n=49). *Lethargy* = 26.16% (n=45). *Poor bone strength* = 18.60% (n=32). *Delayed development* = 12.79% (n=22). *Neurological problems (that may include seizures)* = 9.88% (n=17).

We also asked an open ended question: **How do symptoms and problems associated with PKU impact your day-to-day life and your quality of life?** A sample selected from 192 comments follows:

- *We don't manage Pku around our lives, we manage our lives around Pku.*
- *They (symptoms) affect my ability to function in day to day life in almost every aspect. Common areas at work are in my ability to retain written or verbally communicated information. Severe deficits in short term memory have direct impacts on my ability to perform job responsibilities. Socially, the presence of toxic phenylalanine in my brain affects my ability to establish and maintain relationships with other people. Others often wonder why I can't keep up with conversations or maintain a consistent type of mood or emotional level of stability. Kuvan has essentially taken the computer of my brain and removed the virus, allowing me to tap into my true potential in every area of my life.*
- *I'm impacted by being too tired very often to do much aside from work. I recently found a job through the Council of Disabilities after being out of work for 6 years. I lost a few jobs very shortly after getting them because it was taking too long for me to learn new tasks. I have trouble focusing and forming words sometimes. My hands shake a bit quite often. I don't always weigh my food as it takes a long time as my Math skills are very poor. I need to exercise regularly so I don't hurt myself lifting things. I have a very hard time maintaining muscle mass. I also have problems maintaining my weight. Someone else is typing this as my spelling is also very poor.*
- *Significantly impacts my everyday work and social life. Have to plan way in advance for any activity involving food, and must sacrifice time in the evenings and on weekends preparing, cooking, packing, and ordering low protein foods.*
- *School was a challenge, hard to stay focused. Parents had to break down requests by asking one task at a time. Not good in sports, not very coordinated*
- *The blood testing and clinic appointments take time and cannot be done over the weekend (which affects my ability to work).*
- *I suffer from anxiety and depression and it affects everything I do including, socializing, employment and family. I can't drive due to my anxiety and that is a real problem with a family and it's hard to get my kids to school and to their extracurricular activities, not to mention just doing daily errands. I went to university but couldn't continue to teachers college due to my anxiety and lack of mobility. Sometimes it's hard to concentrate and I have a poor memory.*
- *There isn't a day that goes by that we can just sit back and not plan around PKU meals. At a restaurant, going to a friends, birthday parties... there is always something to bake/cook. At school there is an EA that works with our daughter full-time, another EA does her formula via G-Tube and a family/school liaison works with her on her social skills. We have a team of professionals (OT, Speech Path, and Psych) that we work with constantly at home to support our daughter in all areas of development. There is a high level of stress within our family because of her behaviours.*
- *social situations are extremely intensive to prepare for and I often am left out of these by others. A huge impact is the amount of time I have to spend managing my diet to protect my brain from damage...*
- *Anxiety made it difficult to stay at Post Secondary school so my daughter dropped out after 3 months*

Conclusion: PKU has enormous impact on a person's intellectual development, social inclusion, academic and career achievement, emotional well-being and interpersonal relationships. Patients experience many cognitive problems including deficits in executive functioning, memory, planning,

attention, organization and mental processing speed -- even with well-managed blood-phe levels. Mood disorders and behavioural problems are prevalent. Early diagnosed, diet-compliant patients will have lower IQs than siblings.

2.3 Patients' Experiences With Current Therapy

Since 2000, the gold standard for PKU is diet/treatment for life. Unlike with Kuvan there has never been a randomized control trial of the PKU diet. Except for the mildest version of this enzyme deficiency, this means a lifelong adherence to a low-phe diet that is extremely limited in natural protein, along with supplementation of a phe-free amino acid synthetic formula to meet protein and nutrient needs. The PKU diet is one of the most restrictive diets known, and amounts to an extreme burden of treatment. A major challenge in managing PKU is adherence to the prescribed diet as it is extraordinarily complicated, with limited selection, requiring painstaking efforts in preparation, record-keeping and blood testing.

Further, it lacks variety, satiety and is quite unappetizing. It is particularly burdensome for children and adolescents because the diet serves to isolate them from their peers. As young patients are exposed to the conventional diets of their peers, and begin to compare to the extreme limitations of their own nutritional regime – diet discontinuation becomes inevitable for many.

Patients/caregivers were asked to rate the level of effort required to adhere to a diet restricted in Phe (as prescribed by a physician) on a scale of 1 – 5, 1 = "no effort" and 5 = "much effort", (n=216). The overall weighted average was 4.37. When **clinicians** were asked the same question, the overall weighted average was 4.63, indicating that patients/caregivers and clinicians all recognize the extreme difficulty this diet poses.

We also asked patients/caregivers: **“What are the main issues that affect adherence to the diet?”** (5 choices, “pick all that apply”) (n=196). *Difficulty in pre-planning meals* = 76.02% (149). *Too time-consuming* = 69.90% (137). *Unpalatable/Unpleasant food* = 64.80% (127), *Too expensive/financial burden* = 57.14% (112). *Too complicated* = 29.59% (58). *Do not see value in diet* 2.04% (4).

When we asked: **How do symptoms and problems associated with PKU impact your day-today life and your quality of life?** Many of the comments pertained to experience with current diet therapy:

- *As a mom I stayed home with my daughter. I couldn't trust day care to be as diligent with her diet as myself. All it would take is for to eat 1 chocolate chip cookie and she would be off diet for 2 days. or 1 ice cream cone and she would not be able to eat anything else for a week. I was very strict with her diet and it was all consuming. McDonald's birthday parties I would cut fries into 2 inch pieces and count out 20 of them knowing that was her lunch allotment. If she didn't eat her school lunch I would sit in the car with in the parking lot until she finished it all. I had to run her formula to her if plans changed at school or activities because she could wait till she got home to drink it or she would start shaking.*
- *... I cannot be separated from my son for more than a few hours because everything revolves around his diet. With another child, you could have a babysitter and walk out the door, knowing they will provide something in the house to eat. This is impossible for a parent with PKU. Everything would have to be weighed and calculated before leaving. Anything he doesn't eat, also has to be weighed and calculated. To expect someone without knowledge of PKU to handle this would be impossible. A parent's life must change when they have a child, but this changes your life on a whole other level. Weighing formula and food, calculating phe/protein, logging data, communicating with the dietician or psychologist, ordering food and formula, administering medication, drawing blood and recording*

phe levels all consume a large part of the day. Working full-time as a Resource teacher and managing this diet, leaves very little time for other things. As a competitive athlete in multiple sports, exercise was always a priority. Now my son's health is the priority- leaving very little time for anything else. Our son is an only child. Without PKU and the chances of having another child with PKU (1/4), we would have likely had a larger family. PKU has affected all parts of our lives and the decisions we have made and will make.

- It impacts our lives significantly. Our relationships have all dwindled and we miss out on various family things, ie. Nieces and nephews sporting events etc, because the diet is so challenging and anything that runs into dinner time is just too challenging to partake in. We find day in and day out to be a struggle. We stress all the time, we think about Pku all the time, and our life revolves around it. I do not volunteer anymore, I requested a job change because of the stress and responsibility and time that the diet takes, I do not get a chance to work out because we are up late every night preparing food/lunches/formulas for the next day for our pkuers-it's insane-I don't know how we do it, and I don't know how we will be able to sustain this and have a happy life.*
- The meticulous and rigorous PKU traditional diet is all-consuming: everything the patient potentially eats or drinks could be a poison to his brain. The fear of brain damage never goes away.*
- Dietary restrictions disrupt my teen's social life - making it hard to go out to eat with friends and feel part of the group*
-It's hard for anyone to stay on a special diet long term, no matter what the reason is, especially one that is so restricting and often keeps you from socializing and makes you feel like the odds person out most of the time. Not to mention all the time it takes to prepare separate meals and food constantly and calculate everything you ingest on a daily basis.*
- [REDACTED] will sometimes choose not to attend a social event or eat out with family because he "can't eat anything anyway". He has declined to participate in some opportunities away from home because it would be too hard to maintain his diet and drink his formula.*

Conclusion: Existing diet therapy is not completely effective. The highly restrictive diet is a heavy burden of treatment. Dietary compliance needs to be recognized as a serious disease management issue. A 2013 study in the USA found that 71% of adults with PKU diagnosed at birth were no longer in active clinical treatment. That is a measure of the burden of diet treatment, and quite possibly the effects of poor management as being actively engaged in clinical care requires planning, organization and other executive functions that may have been compromised. Diet discontinuation results in higher Phe levels which is associated with poorer school or work performance, along with increased behavioural problems and mood disorders. Recognizing that keeping the phe level low is critical in the management of PKU, many patients require treatment alternatives, or, at the very least therapeutic options in conjunction to the prescribed diet.

2.4 Impact on Caregivers

Caregivers routinely reported on the anguish they feel on behalf of their children/grandchildren/siblings due to the dietary and lifestyle restrictions and complications PKU patients have to endure. With very high frequency, they reported on how PKU has severely limited their ability to travel, socialize, be spontaneous, go to restaurants, volunteer or otherwise participate in community events along with the tremendous effort and time spent on preparing, ordering, and measuring foods, monitoring food intake, dealing with mood issues, supporting academics, managing clinic appointments, blood tests and other PKU related issues and tasks. A large number reported having to give up full-time employment, or the

heightened stress related to maintaining employment while managing the emotional, behavioural, educational, medical and physical needs of a PKU patient -- in addition to other family responsibilities.

We asked the open ended question: **What is your caregiver experience with PKU? (a) How has PKU affected your daily routine or lifestyle? (b) What challenges have you had to deal with related to symptoms of PKU in the person under you care?** The following is a sample selected from 172 responses, (includes pertinent *caregiver* responses to the open ended question: **How do symptoms and problems associated with PKU impact your day-to-day life and your quality of life?** identified with “*”):

- *My son was adopted through foster care because his birth parents could not manage his PKU.*
- *... We are constantly thinking about our daughter's growth, what food to make, how to make it, whether she can handle that much phe, if she's getting enough calories or if she will even like it. We worry about her phe levels and how they affect not only her brain but, also her behaviour. Blood draws are traumatic and have created an issue with how she handles all medical professionals. She had to have an NG tube placed for formula intake and when she flat out refused to take her formula a G-Tube was surgically inserted. When we bring someone in to take care of our kids we have to train them on PKU, her medical foods, prescriptions and how to calculate phe. When we travel we have to worry about what she can eat, if anything. We travel with vast amounts of medical foods, formulas and equipment. We do everything we can to keep her healthy because with illness comes high phe levels. We deal with a little girl that's moods swing CONSTANTLY, it is a roller-coaster ride that she sometimes cannot help or get off of. PKU is a constant in our life, there is no reprieve*
- *PKU care is extremely expensive and cumbersome. It takes lots of time daily to really maintain it properly. I quit my job 14 years ago to manage his diet and ultimately teach him his diet.*
- *Our son struggles significantly with behaviour (i.e., aggression, emotional regulation) and show symptoms of hyperactivity and inattention. Our clinical team has already started preparing us for the possibility that he may meet criteria for an Anxiety Disorder or ADHD, and he's only 3.5 years old.*
- *... My youngest child has always struggled with her diet, even when controlled at home her levels were higher than we wanted. Now as an adult she continues to have problems. She had learning disabilities and was unable to retain information particularly basic math - we had testing done and got her additional help. She has also been diagnosed with osteoporosis and has thyroid issues which she is being monitored for. Last year she became pregnant and control was only successful after the third month. Sadly the child had multiple issues and died six weeks later - we have struggled with her recovery and the loss.*
- *....We were introduced to a life of weighing every little thing our little guy consumes, watching every mg of phe, and our vacations now include an extra suitcase that contains only medical food. We can no longer enjoy a leisurely dinner out, without packing a lunchbox for our son.*
- *Our social circle has decreased as we don't have the time to participate in as many things and some people are scared to invite us over as they don't know what to serve. We don't travel much anymore as it is too difficult. We have selected activities carefully to avoid too much outside "food".....*
- *....We always have to think about my son's needs first. b) Staying vigilantly organized with regards to insurance reimbursement, clinic visits, home blood tests, meal/calorie phe tracking, ordering food, cooking special/separate food, always carrying meals, snacks, sweets, drinks for absolutely every occasion that involves food. Also his formula must be taken 3-4 times a day. This is a constant challenge because he does not like it and also just to make sure he has it with him when he needs it under ALL*

circumstances no matter where he is, school, travel, visiting, sports, etc. It is something you must stay on top of constantly - no breaks.

- We measure everything our son eats and do math at every meal. We cancel plans to ensure he's eaten, if it's a slow eating day. We haven't put him in daycare or preschool because we've been frightened they'll allow him to have something he shouldn't. If he doesn't eat every 3-4 hours, he becomes hysterical: hitting his head against items, screaming and laughing, hitting, etc. until he has his medical formula. Once he drinks that, he's fine within four minutes.*
- PKU has changed every aspect of our daily lives. We must pay attention to every bite of food consumed by our PKUer. We must pre-plan every meal and snack. We must coordinate in advance with party hostesses, schools, and family for every gathering....*
- Had to quit full time employment to care for my son adequately. **
- I chose to stay home partly to better manage her PKU - one income for the last 8 years has left our family in severe debt. [REDACTED] is anxious than most of her peers and also has trouble doing things as the same speed as her peers, which has caused difficulties with school work. **
- Sometime I feel that the level of care required for our PKU daughter means that our non-PKU daughter becomes neglected.... **
- The incredible amount of supervision required DAILY for us to ensure our 3 year old eats only her food, never shares any of her food, never throws-out any of her food, never leaves food anywhere and forgets about it, is over and above the impact of record keeping, preparing of food, calculations required for each food for the daily running record. **

Conclusion: Caregivers of children and young adults with PKU bear tremendous economic, physical, social and emotional burdens. Always concerned with the potential for neurocognitive and behavioral impacts of ingesting Phe, there is persistent stress and anxiety. Constant vigilance and effort is required to both facilitate the diet, and to prevent any diversions from the diet. The economic costs are frequently enormous with caregivers often having to give up employment, along with having to bear the added costs of a highly specialized diet. Social lives and recreation are often forfeit due to the difficulties of the diet.

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

Information was gathered from the results of two online surveys (See section 2.1). Recognizing that Kuvan has been available in Canada since 2010, in the U.S.A. since 2007 and in Europe since 2008, CanPKU was able to focus on the real world experiences of 127 patients who have used the drug Kuvan.

3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had With the New Drug?

In many PKU patients, Kuvan can substantially correct the metabolic error in the phenylalanine hydroxylase enzyme and thereby lower phe levels. Many patients report, that Kuvan, beyond lowering blood phe levels, also has enormous positive impact on quality-of-life through the opportunity for some (and in certain cases complete) diet normalization. It cannot be overstated how diet normalization positively impacts patient outcomes, and the lives of patients and their caregivers.

We asked: With 1 being "no improvement" and 5 being "significant improvement" please indicate how you feel Kuvan has improved the management of your PKU? (n=121). Weighted average was 4.17. 62.8%

(n=76) rating it a “5”, and 16.5% (n=20) rating it a “4”. Only 10.74% (n=13) reported “no improvement”. A sample selected from of 66 appended comments:

- -she went from an average student through 3 yrs of college to a 3.9 GPA in her 4th yr because of the ability to focus and she is able to absorb and process new information. Drastically lowered anxiety, very little shaking and no irritability. She is sleeping much better too. Kuvan is a Godsend, I wish she could have had it at a younger age. who knows what her potential may have been.
- -KUVAN has been life changing, his protein intake tripled and his blood phe dropped in half. If we had a guarantee access to Kuvan for life he would no longer require formula. Kuvan is at cure level for my son, but without belief in access for life we have no choice but to continue him on the diet
- -█████ is now on a normal diet. Yes that means he can eat whatever he wants and doesn't have to count Phe's (he can now eat anything including meat, seafood pizza, anything).He doesn't have to drink his formula either. He is now thinking better and growing better and is feeling more like everyone else. We only have to go for blood work once a month and his blood Phe numbers are always right on and not fluctuating up and down. █████ would be devastated if he had to go back on diet. Also █████ is now an A student looking to go to university.
- -Taking KUVAN has consistently lowered my daughter's PHE levels to a safe range and increased her tolerance of PHE. I would also argue that she is now thinking more clearly, reacting more quickly mentally and performing better academically.
- -I felt better on Kuvan, more stable and steady. My doctors increased my Phe intake by double greatly easing the difficulty involved in managing the diet.
- -Kuvan was the best thing to happen to me. My levels stayed high no matter what I did. After starting kuvan my levels came down and stayed down and my allowance of phe tripled. ...

We asked: **What side effects (if any) have you experienced using Kuvan?** Pick all that apply. (List: Stomach Pain, Headache, Nausea, Diarrhea, Feeling Agitated, Runny or Stuffy Nose, Cough, Vomiting, Joint Pain, Dizziness and Other). While 89 individuals did experience some of side effects provided in the list, they were reported as typically mild, and often disappearing with use. The top category selected was “Other”=57.7% (n=49). The survey required that anyone selecting “other” provide an explanation. 32 of the 49 (65%) explained that they had no noticeable side effects so they could not select from any of the side effects that were listed as options. This amounts to 38% of all patients reporting no noticeable side effects. 8 of the 49 mentioned heartburn, GERD, Acid Reflux or Stomach discomfort, with 3 of those 8 further explaining that these side-effects soon disappeared. In reference to method of administration, 2 of 49 mentioned problems with pill burden. Another 2 of 49 mentioned mild injection site rash. One individual mentioned slight sleep disturbance, and one thought mild hyperactivity might be attributable to the medication. Of the other side effects selected in the offered list, respondents reported: Stomach Pain= 30.59% (n=26), Headache 11.76% (n=10), Nausea 10.59% (n=9), Diarrhea 7.06% (n=6), Feeling Agitated 7.06% (n=6), Runny or Stuffy Nose 5.88% (n=5) Cough 5.88% (n=5), Vomiting 3.53% (n=3), Joint Pain 3.53% (n=3), Dizziness 2.35% (n=2).

Tellingly, when further asked: **Were any of the side effects you listed above serious enough that you stopped using Kuvan?** (n=102) 94% (n=96) responded “No”, and only 6% (n=6) responded “Yes”.

We asked: **Are there any other benefits/Quality of Life improvements as a result of taking Kuvan that are not directly related to the lowering of blood-phe levels?** 96 individuals responded. Most responses referred to the tremendous QoL impacts of minor or significant diet normalization as a result of Kuvan -

including better overall nutrition, more food choices, and opportunities for normal socialization. Many respondents were unrestrainedly grateful of the beneficial cognitive impacts of taking Kuvan, often mentioning improved academic performance, executive functioning, and focus, along with the newly found belief that their children (or self) could now succeed in post-secondary education, careers, and life in general. Many comments highlighted the improvements in mood and behaviour as a result of Kuvan. Many caregivers reported that they had reduced financial burden as a result of less reliance on medical foods. Here is a sample of comments:

- *Enhanced memory short term and long term increased confidence in social atmospheres. Increased marks in post secondary education. Promotions at work and improvement of ability to carry out job responsibilities. Flexibility in managing diet. No restrictions whatsoever. Ability to improve physical fitness and conditioning. Higher level of focus and attention to detail Improvements in multi tasking ability. Higher energy levels in day to day activities. Critical thinking benefits*
- *Kuvan has been a game changer for our family. It has made an impossible diet more manageable. The diet is still challenging, but the amount of choices our pkuers have now for food, that never would have been possible without Kuvan, is incredible. Our children can eat more food, they can eat healthier food, they can eat normal food-all things that are so much better for their bodies and minds than the synthetic low protein products they had to eat before. I cannot imagine life without Kuvan-I feel like our children stand a chance at maintaining their 'diet for life' prescription because of Kuvan. If they didn't have Kuvan I don't know how they would be able to sustain this awful diet, even with Kuvan they will still face challenges, but Kuvan is that extra push that gives them some normal options and makes the diet possible. The biggest bonus of Kuvan is that when our children are ill, their blood phe levels are %50 lower than when they would get sick prior to being on Kuvan. Kuvan has saved our children's brains, it has prevented brain damage, it has allowed their bodies to ingest and properly digest more real proteins, in turn protecting their organs and assisting with more natural nutrients being absorbed by their bodies.*
- *Mental clarity, improved memory function, able to focus for longer periods of time, substantial increase in amount of protein(and food) that can be consumed in each day, increased muscle mass due to increased food consumption.*
- *Two successful pregnancies*
- *Kuvan has greatly increased my protein tolerance. As a result I'm able to include a variety of regular (non medical foods) food to my diet. I'm also able to eat enough food in one meal to leave me feeling full for a substantial amount of time. Eating enough food to feel satiated between meals was a problem for me before I was on Kuvan treatment.*
- *...anxiety and phobia's were greatly reduced as a by-product of taking KUVAN. Kuvan has permitted us to have a much more relaxed approach to his diet which has huge impacts on his social life. He can now join in with others without standing out which for a 13 year old is a very important aspect of a teen's life...With Kuvan I believe he can attend university out of province, or home town, ...*
- *Kuvan seemed to help stabilize my Phe throughout the day. I felt more stable and steady overall. I didn't feel lows and highs.*
- *..Kuvan has at least doubled [REDACTED]'s phe tolerance. This means we are less reliant on expensive, difficult to absorb low-protein foods. The increased natural protein is better for her body and brain. It has also allowed us to manage her PKU in a different way: we no longer have to weigh any fruits, 'garden' veggies or low protein foods. This allows us to engage in social situations with much more*

ease. Throughout all of these benefits, her levels have become lower and more stable than her pre-Kuvan levels.

- Virtual elimination of signs of a learning disability and major increase in processing speed and major increase in abilities to focus and concentrate.....
- [REDACTED]'s outlook on life has improved. He is social and very active. He enjoys teaching and performing in dance competitions. -He is more affectionate and enjoys physical contact now that he is taking Kuvan - He went from failing math class to getting 84%! His other classes in school also showed improvement - He is more organized and completes homework independently -His anxiety and fears (heights, lighting storms, germs) have completely disappeared! -No longer constantly bites his nails, or washes his hands excessively (his hands were red, dry and bleeding) -He is more calm, relaxed, cooperative and gets along better with his siblings

We also asked: **Is there anything else about your experience with Kuvan that you would like us to know and include?** A selection of responses is here:

- Kuvan stopped my shaking hands and if I forget to take my kuvan I go through withdrawals such as mood changes, agitation, seizures, etc.
- we are very worried and saddened to think that in 6 months we may not be able to afford Kuvan and our daughter will be taken off a drug that has potentially opened up her life to success in so many ways. Mentally Physically Emotionally. It is devastating to know that there is a drug available like this and we can't have access to it; then to watch your child regress to the shell she was without it. There are no words.
- I've responded well to kuvan and it has changed my life i can go out for dinner with my girlfriend without an hour of prep/research, my quality of life is drastically improved but i look anxiously into the future as i will only recieve kuvan through insurance for a few more years after that the plethora of social mental and physical problems i had may come back and that scares me.
- It is truly a life changing drug for my son, it is a cure level for him and its such a shame we can't fully embrace this due to the lack of security with accessing Kuvan for life. Others in the PKU community have the attitude that unless access is secured they aren't willing to try it.We weighed the risk/rewards and decided that kuvan especially in his high risk years (teens) outweighed the downside risks of lack of access to drug in his adult years..... Kuvan is life changing and increases his chances of success in such a profound way I believe it is worth it to go forth believing it will eventually covered by our public drug plan.
- Her clinical trial ends in August. After that, our only option is private insurance - our current plan does cover Kuvan, but if my husband loses his job, or the company changes the plan or we reach the \$1 million lifetime limit, then we suddenly do not have access any more. With one of the huge benefits to Kuvan being a more natural diet, we need our provincial government to provide back up funding for patients that lose or do not have private insurance!
- Kuvan has been a life saver for my son, I worry about what the future holds for him once he is off our private insurance plan. The goal was to get him through high school I know, but I want him to continue to enjoy life, not feel ashamed to have PKU and left out, to hate his PKU. I worry he will go back to having strong anxiety and not be able to have a career

Conclusion: Kuvan, in many patients, is life-changing and can lead to important reductions in blood Phe levels. From the patient perspective, the outcome of greatest importance with respect to treatment is

the ability to eat a more normal diet while avoiding the adverse consequences of increased blood PHE level. The normalization of diet (associated with use of Kuvan) is expected to improve quality of life for patients as well as decrease the financial burden on patients and their families. For patients with poor dietary compliance, responders to Kuvan will offer a much needed treatment option.

Section 4 — Additional Information

Key Factors Contributing to Treatment Choice & Obstacles to Best Outcomes

In our survey of Physicians, we asked about prescribing decision methods. Here are some key results from that survey:

We asked: **In determining pharmacotherapy for patients, which do you believe supports the potential for best clinical outcomes: (pick one):** 1. Provincially-prescribed drug reimbursement/eligibility criteria or 2. Physician-Patient choice in selecting and/or tailoring drug therapy. **All (100%) selected “Physician-Patient choice in selecting and/or tailoring drug therapy.”**

We also asked physicians: **With 1 being “not qualified” and 5 being “very qualified”, based on your assessment of “significant clinical benefit”, please rate how qualified you believe you are to determine if a patient would be a good candidate for continued treatment with Kuvan?** (n=7) Weighted average = 4.86. Physicians believe themselves expert at determining good candidates for continued treatment.

We asked treating physicians: **In your opinion, what types of PKU patients should be offered a trial of Kuvan to assess responsiveness?** Note: all answers assume that patients with the two mutations, known or predicted to completely abolish PAH activity, are not suitable for a trial of Kuvan.

Four options were offered: 1. Patients with mild PAH deficiency (Hyperphe) 2. Patients with moderate PAH deficiency (Mild PKU) 3. Patients with severe PAH deficiency (Classical PKU) or 4. Patients with mild, moderate and severe PAH-deficiency (all of the above). Six (6) physicians answered the question with **ALL (100%) selecting “Patients with mild, moderate and severe PAH-deficiency (all of the above)”**

We asked treating physicians: **With 1 being “not important” and 5 being “very important”, if Kuvan provides your patients with the opportunity to normalize their diet, how important is the issue of long-term funding guarantees for Kuvan before patients are willing to implement more normalized diets?** (N=7). Weighted average = 4.86. Physicians strongly believe long-term funding guarantees are very important for their patients.

Progress in Canadian Access to Kuvan

While a re-review of Kuvan is still pending by CDEC – the fourth time Kuvan will have been considered by CDEC since 2010 - and while PKU patients across Canada desperately await fair access to the only available pharmaceutical treatment for their disease, there has been some movement to improve access to Kuvan in certain Canadian jurisdictions.

Health Canada confirmed it has signed an agreement with BioMarin for Kuvan to cover indigenous populations with PKU. This is the third Common Drug Review participating drug plan to sign an agreement. Quebec was the first to provide access to Kuvan including an open listing for women with PKU who are pregnant or considering a pregnancy and exceptional access on a case-by-case basis.

The access criteria adopted by ON, SK and recently by Health Canada are not based on the best available scientific evidence. We urge CDEC to pay attention to the two letters written by the group

of PKU treaters in Ontario to the ON drug program dated March 2014 and November 2015. These letters include the scientific evidence for the clinical benefits of sustained control of neurotoxic levels of blood phe. We also urge CDEC to pay attention to the revised criteria published by the State of California in 2015 which significantly alters the original criteria of that jurisdiction published in 2009. The ON physicians' letters and the California criteria are public documents which we are happy to provide on request.

We and treating physicians have been unable to engage in a meaningful discussion with public drug plan managers outside Quebec about evidence-based criteria. We continue to be disappointed that most of the CDR drug plans chose to ignore the comments of CDEC in the "of note" paragraph on Page One of its reports in 2010 and 2011.

Therefore we request CDEC to go further than it did in 2010 and 2011 by providing explicit advice on clinical criteria based on the input of patients and caregivers summarized in this submission and based on the input of clinical experts in PKU.

Conclusion: Across Canada and around the world the diagnosis and treatment of PKU is built on the foundation of measuring and managing neurotoxic levels of phe in blood based on clinical experience and much other evidence.

CanPKU urges CEDC to align with the growing recognition by various Canadian jurisdictions of Kuvan's significant clinical value and provide advice on access criteria which recognize the distinctive clinical benefits individually of:

1. lowering neurotoxic levels of phe in blood, or
2. increasing levels of natural protein and decreasing levels of synthetic protein in the PKU diet, or
3. age-appropriate, measureable improvements in neurocognitive/neuropsychological functions, or
4. age appropriate, measureable improvements in quality of life.